PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
PAC/AGS/23361 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/004487	21.10.2004	23.10.2003

International Patent Classification (IPC) or national classification and IPC
A61K9/70, A61K31/568

Applicant
CIPLA LIMITED

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23.08.2005	21.12.2005

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Schifferer, H

Telephone No. +49 89 2399-7472

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/004487

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-9 as originally filed

   Claims, Numbers

   1-20 filed with telefax on 31.10.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/004487

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-20
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

V Reasoned statement under Rule 66.2 (a) (ii) with regard to novelty, inventive step or industrial applicability

1) Amendments - Article 19 (2) PCT
The amended set of claims 1-20 is considered acceptable according to Article 19 PCT and covered by the application as originally submitted.

2) Clarity - Article 6 PCT

2.1) Claims 5,13, 15, page 4, lines 8, 9, 33, page 5, lines 14-18, page 5, lines 27-30, page 6, lines 3, 4, page 6, line 15 use the word "about" for defining the corresponding weight percentages. According to PCT International Preliminary Examination Guidelines Chapter III 4.5 a) and Article 6 PCT, this expression lacks clarity, since its exact meaning and range which should indeed be anticipated are left unclear.

3) Documents
The following documents (D1-D6) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO 88/09185 A (BURGHART, KURT; BURGHART, WALTER) 1 December 1988 (1988-12-01)
D2: US 6 010 716 A (SAUNAL ET AL) 4 January 2000 (2000-01-04)
D3: WO 00/45795 A (CIPLA LIMITED; WAIN, CHRISTOPHER, PAUL; LULLA, AMAR; MALHOTRA, GEENA;) 10 August 2000 (2000-08-10)
D4: DE 102 11 832 A1 (LTS LOHMANN THERAPIE-SYSTEME AG) 2 October 2003 (2003-10-02)
D5: US 6 007 835 A (BON-LAPILLONNE ET AL) 28 December 1999 (1999-12-28)
D6: US 2004/213744 A1 (LULLA AMAR ET AL) 28 October 2004 (2004-10-28)

Unless otherwise specified, reference is made to the respective cited passages in D1-D6 (see the International Search Report, Form PCT/ISA/210).

4) Novelty - Article 33 (1) and (2) PCT

4.1) The subject-matter of the amended set of claims 1-20 may be considered novel, since their content is not explicitly and unambiguously disclosed by D1- D6. The transdermal spray formulation in present application was specified by the introduction of the important components in terms of their quantity and quality and by the specification of the vehicle for being a solvent. D1-D5 succeed in demonstrating the categories of components, however, their quantity is at least with one limit far away from that disclosed here. For a detailed elaboration of the differences between the amended claims and the documents D1-D5 it is referred to the corresponding passages of the telefax of October 31st, 2005.

5) Inventive Step - Article 33 (1) and (3) PCT

5.1) The problem posed in the present application was a transdermal drug delivery formulation avoiding the following disadvantages: a) expensive to manufacture, b) reduced adhesion to the skin, c) irritation after patch removal, d) disposal problems, e) use of water-soluble drugs only possible, f) easy involuntary

removal of gels after application.

The solution according to the Applicant was a pharmaceutical transdermal therapeutic spray composition comprising an active ingredient, 0.1%-2.0% by weight of a vinylpyrrolidone/vinyl acetate copolymer and at least 60 % by weight of a non-aqueous solvent.

D1 which is regarded closest prior art discloses a transdermal, therapeutically active pharmaceutical preparation which is administered via a spraying nozzle and which comprises the following components: a) a polymer which forms a film (vinylpyrrolidone/vinylacetate copolymers and polymethacrylic acid butyl ester; 3:1 - 1:3, b) an active agent, such as estradiol, fentanyl, c) a solvent influencing drug release, such as paraffine, sorbitan macrogol laurate, fatty acid di- or triglycerides, propylene carbonate, d) a solvent evaporating on the skin (dichlormethane, ethanol, ethylacetate, isopropanol).

D1 does not disclose

- the use of an anti-nucleating agent, such as polyvinylpyrrolidone polymer or copolymer
- the penetration enhancers menthol, dimethylisosorbide, glycerylmono-oleate, myristyl lactate
- the percentage of the solvent of at least 60 %.

Unexpected or surprising effects do not seem to be connected with this kind of inactive ingredients and their quantity.

As already written in the letter of October 31st, 2005, a solvent and a propellant (78 % in total; 14.3 % solvent) have been used in the composition disclosed with D1.

When aiming at a propellant-free formulation, the closest step seems to be to fill up the quantity of the propellant with the solvent, in order not to change the final concentrations of the active ingredient and the dosage. Therefore, there may be some evidence for present composition in the amended form for the person skilled in the art.

5.2) It appears to be obvious to a person skilled in the art to formulate a composition comprising the components listed in terms of their quality and quantity on the basis of the teaching of D1, common galenical experience and textbook knowledge, since unexpected or surprising effects are not given with said type and quantity of inactive agents. Thus the aforementioned subject-matter of claims 1-20 in the amended form does not meet the requirements of Article 33 (1) and (3) PCT in that extent that it cannot be considered inventive.

VI) Certain documents cited

On the basis of rule 70.10 PCT certain published documents - namely those published after filing /priority date of present application (Rule 64 (3) PCT) - should be mentioned as such. This refers to D6 demonstrating the following details:

Application No: 10/686,517
Patent No: US2004/0213744
Publication date: 28.10.2004
Filing date: 16.10.2003
Priority dates: IN2000MU00044 - 13.01.2000; IN1999MU00382-20.05.1999;IN1900MU00582 - 17.08.1999; IN2000MU00043 - 13.01.2000

D4 discloses a sprayable composition for topical application comprising 0.0001-30 % of at least one medicament (estradiol, steroids), a permeation enhancer (menthol, lipophilic solvents), at least one film former (povidone vinyl acetate), and at least one vehicle (aqueous or non-aqueous vehicle). The composition forms a stable film following its application on the cutaneous surface. When comparing with the amended set of claims, D4 lacks the explicit and unambiguous disclosure of the transdermal spray composition as summarised with the altered claim 1 of October 31st, 2005.

CLAIMS:

1. A transdermal spray formulation comprising:
   a) a pharmaceutically active agent;
   b) 0.1% to 2.0% by weight VP/VA copolymer;
   c) at least 60% by weight of a non-aqueous solvent; and
   d) optionally a penetration enhancer, which, if present, is present in and amount of 0.01% to 5.0% by weight of the composition

2. A transdermal spray formulation according to claim 1, wherein the pharmaceutically active agent is provided in a therapeutically effective amount.

3. A transdermal spray formulation according to any preceding claim, further comprising an anti-nucleating agent.

4. A transdermal spray formulation according to claim 3, wherein the anti-nucleating agent is a polyvinylpyrrolidone polymer or copolymer.

5. A transdermal spray formulation according to claim 3 or 4, wherein the anti-nucleating agent comprises from about 1% to about 10% by weight of the formulation.

6. A transdermal spray formulation according to any preceding claim, wherein the penetration enhancer is a monohydric alcohol such as ethanol, isopropyl, butyl and benzyl alcohol; a dihydric alcohol such as ethylene glycol, diethylene glycol, propylene glycol, dipropylene glycol or trimethylene glycol; a polyhydric alcohol such as glycerin, sorbitol and polyethylene glycol; a polyethylene glycol ether of an aliphatic alcohol, such as cetyl, lauryl, oleyl and stearyl, including polyoxyethylene (4) lauryl ether, polyoxyethylene (2) oleyl ether, polyoxyethylene (10) oleyl ether or polyoxyethylene alkyl ether; vegetable, animal or fish fats or oil such as olive and castor oils, squalene or

lanolin; a fatty acid ester such as propyl oleate, decyl oleate, isopropyl palmitate, glycol palmitate, glycol laurate, dodecyl myristate, isopropyl myristate and glycol stearate; a fatty acid alcohol such as oleyl alcohol and derivatives thereof; a fatty acid amide such as oleamide and derivatives thereof; urea and urea derivatives such as allantoin; a polar solvent such as dimethyllaurylamide, dodecylpyrrolidone, isosorbitol, salicylic acid, an amino acid; a higher molecular weight aliphatic surfactant such as lauryl sulfate salts or esters of sorbitol and sorbitol anhydride; polysorbates 20, 21, 40, 60, 61, 65, 80, 81, or 85; oleic and linoleic acids, ascorbic acid, panthenol, butylated hydroxytoluene, tocopherol, tocopherol acetate, tocopheryl linoleate, menthol, dimethylisosorbide, glycerylmono-oleate or myristyl lactate.

7. A transdermal spray formulation according to any preceding claim, wherein the penetration enhancer is selected from the group consisting of menthol, dimethylisosorbide, glycerylmono-oleate and myristyl lactate.

8. A transdermal spray formulation according to any preceding claim, wherein the non-aqueous solvent is volatile and evaporates at mammalian skin temperature.

9. A transdermal spray formulation according to any preceding claim, wherein the non-aqueous vehicle is one or more of ethanol, acetone and methylal.

10. A transdermal spray formulation according to any preceding claim, wherein pharmaceutically active agent is one or more of the following classes: anti-inflammatory drugs, analgesics, anti-arthritic drugs, antispasmodics, antidepressants, anti-psychotics, tranquillisers, anti-anxiety drugs, narcotic antagonists, antiparkinsonian agents, cholinergic agonists, chemotherapeutic drugs, immunosuppressive agents, antiviral agents, antibiotic agents, appetite suppressants, anti-emetics, anti-cholinergics, antihistaminics, anti-migraine agents, coronary, cerebral or peripheral vasodilators, hormonal agents,

contraceptives, anti-thrombotic agents, diuretics, antihypertensive agents, cardiovascular drugs and opioids.

11. A transdermal spray formulation according to any preceding claim, wherein the pharmaceutically active agent is one or more of estradiol, testosterone, oxybutynin, buprenorphine and fentanyl.

12. A transdermal spray formulation according to any preceding claim, wherein the pharmaceutically active agent is estradiol.

13. A transdermal spray formulation according to claim 11 or 12, wherein the estradiol is present in an amount from about 1% to about 5% by weight of the formulation.

14. A transdermal spray formulation according to any preceding claim, wherein the pharmaceutically active agent is testosterone.

15. A transdermal spray formulation according to any preceding claim, wherein the testosterone is present in an amount up to about 16.66% by weight of the formulation.

16. A transdermal spray formulation according to claim 1 for forming a patch on the skin of a subject, wherein the non-aqueous solvent comprises ethanol, methylal or acetone or mixtures thereof; and wherein the optional penetration enhancer, when present, is different to the non-aqueous solvent.

17. A transdermal spray formulation according to claim 16, wherein the non-aqueous solvent comprises ethanol.

18. A method of administering a pharmaceutically active agent, comprising spraying a transdermal formulation according to any one of claims 1 to 17 onto the skin of a subject in need thereof.

19. A method according to claim 18, wherein the non-aqueous solvent volatizes upon contact with the skin, forming a film comprising the VP/VA copolymer and the pharmaceutically active agent.

20. A method of forming a pharmaceutically active film comprising spraying a transdermal formulation according to any one of claims 1 to 17 on the skin of a subject in need thereof.

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